

What is claimed is:

1. An isolated polynucleotide encoding a polypeptide having at least 35% sequence identity to SEQ ID NO:8, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate.

5

2. The isolated polynucleotide of claim 1, wherein the polynucleotide comprises SEQ ID NO:3.

10 3. The isolated polynucleotide of claim 1, wherein the polynucleotide comprises SEQ ID NO:5.

4. The isolated polynucleotide of claim 1, wherein the polynucleotide comprises SEQ ID NO:7.

15 5. The isolated polynucleotide of claim 1, wherein the polynucleotide comprises SEQ ID NO:9.

6. The isolated polynucleotide of claim 1, wherein the polynucleotide comprises SEQ ID NO:11.

20

7. An isolated polynucleotide that hybridizes to SEQ ID NO:1 under stringent hybridization conditions, wherein the polynucleotide encodes a polypeptide demonstrating transmembrane transport of citrate.

25 8. The isolated polynucleotide of claim 7, wherein the polynucleotide comprises SEQ ID NO:1.

9. The isolated polynucleotide of claim 7, wherein the polynucleotide does not comprise SEQ ID NO:1.

30

10. An isolated polynucleotide that hybridizes to SEQ ID NO:3 under stringent hybridization conditions, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate.
- 5 11. The isolated polynucleotide of claim 10, wherein the polynucleotide comprises SEQ ID NO:3.
12. An isolated polynucleotide that hybridizes to SEQ ID NO:5 under stringent hybridization conditions, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate.
- 10 13. The isolated polynucleotide of claim 12, wherein the polynucleotide comprises SEQ ID NO:5.
- 15 14. An isolated polynucleotide that hybridizes to SEQ ID NO:7 under stringent hybridization conditions, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate.
- 20 15. The isolated polynucleotide of claim 14, wherein the polynucleotide comprises SEQ ID NO:7.
16. An isolated polynucleotide that hybridizes to SEQ ID NO:9 under stringent hybridization conditions, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate. ✓
- 25 17. The isolated polynucleotide of claim 16, wherein the polynucleotide comprises SEQ ID NO:9.
- 30 18. An isolated polynucleotide that hybridizes to SEQ ID NO:11 under stringent hybridization conditions, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate. ✓

19. The isolated polynucleotide of claim 18, wherein the polynucleotide comprises SEQ ID NO:11.
20. An isolated polynucleotide encoding a polypeptide having at least 35% sequence identity to SEQ ID NO:6, wherein the polynucleotide encodes a polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate.
21. The isolated polynucleotide of claim 20, wherein the encoded Na⁺-dependent transmembrane transport of citrate is modulated by Li⁺.
22. The isolated polynucleotide of claim 20, wherein the polynucleotide comprises SEQ ID NO:3.
23. The isolated polynucleotide of claim 20, wherein the polynucleotide comprises SEQ ID NO:5.
24. The isolated polynucleotide of claim 20, wherein the polynucleotide comprises SEQ ID NO:7.
25. The isolated polynucleotide of claim 20, wherein the polynucleotide comprises SEQ ID NO:9.
26. The isolated polynucleotide of claim 20, wherein the polynucleotide comprises SEQ ID NO:11.
27. The isolated polynucleotide of claim 20, wherein the encoded polypeptide demonstrating Na⁺-dependent transmembrane transport of citrate demonstrates a requirement for multiple Na⁺ ions for transport coupling.
28. The isolated polynucleotide of claim 20, wherein the transmembrane transport of citrate is electrogenic.

29. A plasmid comprising the isolated polynucleotide of claim 20.
30. The plasmid of claim 29, wherein the plasmid comprises an expression vector.
- 5 31. An isolated host cell comprising the isolated polynucleotide of claim 20.
32. The isolated host cell of claim 31 demonstrating transient expression of the encoded Na^+ -dependent transmembrane citrate transporter.
- 10 33. The isolated host cell of claim 31 demonstrating stable expression of the encoded Na^+ -dependent transmembrane citrate transporter.
34. The isolated host cell of claim 31, wherein the Na^+ -dependent transmembrane transport of citrate is modulated by Li^+ .
- 15 35. The isolated host cell of claim 31, wherein the host cell is selected from the group consisting of human cells, insect cells, xenopus oocytes, and yeast cells.
- 20 36. An isolated polypeptide having at least 35% identity with SEQ ID NO:2, wherein the polypeptide is a transmembrane transporter of citrate.
37. The isolated polypeptide of claim 36, wherein the polypeptide comprises SEQ ID NO:2.
- 25 38. The isolated polypeptide of claim 36, wherein the polypeptide demonstrates Na^+ -dependent transmembrane transport of citrate.
39. The isolated polypeptide of claim 38, wherein the polypeptide comprises
- 30 SEQ ID NO:4.

40. The isolated polypeptide of claim 38, wherein the polypeptide comprises SEQ ID NO:8.
41. The isolated polypeptide of claim 38, wherein the polypeptide comprises
5 SEQ ID NO:10.
42. The isolated polypeptide of claim 38, wherein the polypeptide comprises SEQ ID NO:12.
- 10 43. The isolated polypeptide of claim 38, wherein the Na⁺-dependent transmembrane transport of citrate is modulated by Li⁺.
44. The isolated polypeptide of claim 43, wherein the polypeptide comprises SEQ ID NO:6.
- 15 45. An isolated polypeptide having at least 35% sequence identity to SEQ ID NO:6, wherein polypeptide demonstrates Na⁺-dependent transmembrane transport of citrate. ✓
- 20 46. The isolated polypeptide of claim 45, wherein the encoded Na⁺-dependent transmembrane transport of citrate is modulated by Li⁺.
47. An isolated polypeptide having at least 75% sequence identity to SEQ ID NO:6, wherein the polypeptide demonstrates Na⁺-dependent transmembrane
25 transport of citrate.
48. The isolated polypeptide of claim 47, wherein the Na⁺-dependent transmembrane transport of citrate is modulated by Li⁺.
- 30 49. An isolated polypeptide, wherein the polypeptide is encoded by a polynucleotide that hybridizes to SEQ ID NO:1 under stringent hybridization ✓

conditions and wherein the polypeptide demonstrates transmembrane transport of citrate.

50. An isolated polypeptide having at least 35% sequence identity to SEQ ID NO:8, wherein the polypeptide demonstrates Na⁺-dependent transmembrane transport of citrate.

51. An antibody that specifically binds to the isolated polypeptide of claim 36.

52. The antibody of claim 51, wherein the antibody is monoclonal or polyclonal.

53. The antibody of claim 51, wherein the antibody is derived from a mouse, rat, rabbit, hamster, goat, horse, or human.

54. The antibody of claim 51, wherein the antibody is produced recombinantly.

55. A chimeric protein comprising one or more variable regions from the antibody of claim 51.

56. The antibody of claim 51 linked to a detectable marker.

57. A method of identifying an agent that modifies transmembrane citrate transporter activity comprising:

contacting a host cell expressing a transmembrane citrate transporter polypeptide having at least 35% identity with SEQ ID NO:2 with an agent;

measuring citrate transport into the host cell in the presence of agent;

and comparing citrate transport into the host cell in the presence of the agent to citrate transport into the host cell in the absence of the agent;

wherein a decreased transport of citrate into the host cell in the presence of the agent indicates the agent is an inhibitor of transmembrane citrate transporter activity;

wherein an increased transport of citrate into the host cell in the presence of the agent indicates the agent is a stimulator of transmembrane citrate transporter activity.

- 5 58. A method of identifying an agent that modifies transmembrane citrate transporter activity comprising:

contacting a host cell expressing a transmembrane citrate transporter polypeptide having at least 35% sequence identity to SEQ ID NO:8, wherein the transmembrane citrate transporter polypeptide demonstrates Na⁺-dependent
10 transmembrane transport of citrate;

measuring citrate transport into the host cell in the presence of agent;
and comparing citrate transport into the host cell in the presence of the agent to citrate transport into the host cell in the absence of the agent;

- wherein a decreased transport of citrate into the host cell in the presence
15 of the agent indicates the agent is an inhibitor of transmembrane citrate transporter activity;

wherein an increased transport of citrate into the host cell in the presence of the agent indicates the agent is a stimulator of transmembrane citrate transporter activity.

20

59. A method of identifying an agent that modifies transmembrane citrate transporter activity comprising:

contacting a host cell expressing a transmembrane citrate transporter polypeptide having at least 35% sequence identity to SEQ ID NO:6, wherein the transmembrane citrate transporter polypeptide demonstrates Na⁺-dependent
25 transmembrane transport of citrate and wherein the encoded Na⁺-dependent transmembrane transport of citrate is stimulated by Li⁺;

- measuring citrate transport into the host cell in the presence of agent;
and comparing citrate transport into the host cell in the presence of the
30 agent to citrate transport into the host cell in the absence of the agent;

wherein a decreased transport of citrate into the host cell in the presence of the agent indicates the agent is an inhibitor of transmembrane citrate transporter activity;

5 wherein an increased transport of citrate into the host cell in the presence of the agent indicates the agent is a stimulator of transmembrane citrate transporter activity.

60. A modifier of a transmembrane citrate transporter, as identified by the method of claim 57.

10

61. A modifier of a transmembrane citrate transporter, the transmembrane citrate transporter comprising SEQ ID NO:6.

62. A composition comprising the modifier of claim 61.

15

63. A composition comprising the modifier of claim 61 and a pharmaceutically acceptable carrier.

64. The composition of claim 62 further comprising an additional therapeutic agent.

20

65. The composition of claim 65, wherein the additional therapeutic agent is lithium.

25 66. A method of extending the lifespan in a subject comprising administering an inhibitor of a transmembrane citrate transporter to a subject.

67. A method of weight reduction in a subject comprising administering an inhibitor of a transmembrane citrate transporter to a subject.

30

68. A method of preventing weight gain in a subject comprising administering an inhibitor of a transmembrane citrate transporter to a subject.

69. The method of claim 68, wherein the subject is a human subject.
70. The method of claim 68, wherein the subject is a domestic pet.
- 5 71. A method of lowering blood cholesterol levels in a subject comprising
administering an inhibitor of a transmembrane citrate transporter to a subject.
72. A method of lowering blood triglyceride levels in a subject comprising
10 administering an inhibitor of a transmembrane citrate transporter to a subject.
73. A method of lowering blood LDL levels in a subject comprising
administering an inhibitor of a transmembrane citrate transporter to a subject.
- 15 74. A method of lowering blood glucose levels in a subject comprising
administering an inhibitor of a transmembrane citrate transporter to a subject.
75. The method of claim 74, wherein the subject is a diabetic
- 20 76. A method of identifying an agent that modifies Na^+ -dependent
transmembrane citrate transporter activity comprising:
contacting a host cell expressing a Na^+ -dependent transmembrane citrate
transporter selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6,
SEQ ID NO:8, SEQ ID NO:10, and SEQ ID NO:12 with an agent;
25 measuring the citrate-induced inward electrical current into the host cell
in the presence of agent; and
comparing the citrate-induced inward electrical current into the host cell
in the presence of the agent to the citrate-induced inward electrical current into
the host cell in the absence of the agent;
30 wherein a decrease in the inward electrical current into the host cell in
the presence of the agent indicates the agent is a blocker of Na^+ -dependent
transmembrane citrate transporter activity;

wherein an increase in the inward electrical current into the host cell in the presence of the agent indicates the agent is a stimulator of Na^+ -dependent transmembrane citrate transporter activity.

- 5 77. A method of identifying an agent that serves as a substrate of a Na^+ -dependent transmembrane citrate transporter comprising:

contacting a host cell expressing a Na^+ -dependent transmembrane citrate transporter selected from the group consisting of SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, SEQ ID NO:10, and SEQ ID NO:12 with an agent; and

- 10 determining the entry of the agent into the cell via the Na^+ -dependent transmembrane citrate transporter in the presence of agent;

wherein entry of the agent via the Na^+ -dependent transmembrane citrate transporter indicates the agent is a substrate of a Na^+ -dependent transmembrane citrate transporter.